COMMENTARY

From pharmacokinetics modifying to synthetic biology, non-small molecule therapies for drug addiction

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ABSTRACT

Drug addiction is a widespread issue across the world. It has an impact on the abuser's life as well as the public's health, which is a severe concern. Therefore, there is a significant need for the creation of new, potent treatments for drug addiction. There is a lot of interest in creating alternative tactics that broaden the use of small-molecule-based therapeutics given the limited success of small-molecule medications. By changing the pharmacokinetics of the drug and lowering the concentrations of the drug in the central nervous system, the enzyme catalytic approach and the antibody-based trapping technique have been regarded as viable approaches to lessen the euphoria of drug users.

INTRODUCTION

According to the World Drug Report 2021 published by the UN Office on Drugs and Crime, 275 million people, or around one in every 30 people, used drugs in the previous year. Substance use disorder, generally known as drug addiction, affects about 36 million individuals worldwide. Drug addiction is a long-term, recurrent brain condition marked by intense drug craving and drug seeking, as well as a high rate of relapse in spite of negative effects. Despite the fact that drug misuse is on the rise, only 12.5% of people receive treatment. There is enough proof to conclude that treating drug use disorder is less expensive than doing nothing. In actuality, medication is typically used in conjunction with psychosocial therapies (such as exercise, socialising, hobbies, group sessions, etc.) to treat drug addiction. Pharmaceuticals are administered to treat withdrawal symptoms and to prevent recurrence in some cases. However, due to their low efficacies and detrimental side effects, small-molecule medications (such as methadone, buprenorphine, naloxone, and naltrexone) have only had a limited amount of success (addiction, poor compliance, etc.) There is a lot of interest in creating alternative tactics that broaden the applicability of small-molecule-based medicines in order to address this unmet clinical need. Antibodies have been suggested as a way to minimize the amount of drug in the Central Nervous System and sequester the drug in the blood (CNS). This trapping method favorably changes the pharmacokinetics and distribution of the medication to various organ systems, specifically lowering drug concentrations in the CNS to lessen pleasure, unlike small-molecule therapies that rely on preventing drug binding at specific receptors in the CNS. Drugs lacking euphoric effects are intended to prevent drug-seeking behavior, which should help users stay off the abused substance. Theoretically, the antibody binds and captures drug molecules in a stoichiometric manner. It would be anticipated that a large antibody dosage would sequester the medication in the circulation and prevent saturation. Recently, an enzyme degradation strategy has been put out as a viable therapy method for cocaine and nicotine addiction in addition to antibodies. Before entering the CNS, these psychoactive compounds quickly degrade into inactive metabolites, minimizing brain exposure and lowering the drug's reinforcing effects. The catalytic enzyme-based technique, as opposed to the trapping strategy, could cycle through enzymes to hasten the breakdown of drug molecules. As a result, it appears that the enzyme catalytic approach is significantly more effective than the noncovalent binding-based sequestration technique. It should be mentioned that most medicinal enzymes are derived from microorganisms. Exogenous enzymes typically have short in vivo half-lives and are

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unstable in the body. Exogenous recombinant enzymes have a significant potential to support psychosocial interventions for a substance abuser's transition to a drug-free and abstinent lifestyle, but numerous challenges, like protein instability, short half-lives, and inconvenient administration, still need to be addressed. To date, methods for boosting stability and catalytic efficiency have included chemical modification, directed evolution, computer-aided rational design, and delivery via nanocarriers. Precision genetic engineering for somatic gene therapy is now achievable thanks to the quick development of gene editing technologies, such as the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) system. In addition to enzymes, ex vivo gene therapy using epidermal stem cells may also transport other effector molecules, such as Glucagon-Like Peptide 1 (GLP-1), which blocks GLP-1 receptors in the mesolimbic dopamine pathway to lessen the neurobiological effects of drug dependence. For example, GLP-1 synthesis from skin grafts created using CRISPR-mediated genome editing reduced alcohol-induced dopamine release in the nucleus accumbens and attenuated the resumption of alcohol seeking and voluntary alcohol consumption. Additionally, simultaneous gene therapy expression of BChE and GLP-1 might lessen the harmful and drug-seeking effects of co-administration of cocaine and alcohol. In order to control the CRISPR system for gene editing and enable the precise and reversible transcriptional control of transgene expression, a number of small-molecule (such as fatty acid, sodium ferulate, protocatechuic acid, resveratrol, and caffeine)-responsive gene switches have been established. In order to precisely control the expression of therapeutic proteins to avoid drug addiction, the same method might be used to create programmed gene switches in response to illicit drugs. It might be possible to modulate addiction by the drug itself through the use of synthetic biology. A complex neuropsychiatric illness, drug addiction. Long-Term Depression (LTD), according to mounting research, plays a role in the pathophysiology of drug addiction. Cocaine-induced behavioral sensitization has been shown to be prevented by the use of peptide inhibitors that target the carboxyl tail of the AMPAR subunit GluA2. Drug-induced changes in glutamate neurotransmission are another typical feature of addiction. Kynurenic Acid (KYNA) regulates glutamatergic transmission by interacting with its receptors to mitigate the addictive effects of drug misuse. The primary goal of the current pharmacological approaches to treating addiction is to eliminate the euphoric effects of drug usage. Setting up a conditioned aversion technique to avoid medications could be a revolutionary strategy in light of the advent of CRISPR-based synthetic regulatory circuits. When someone uses drugs, the conditioned aversion is aroused, which then compels them to abstain from the drug of abuse. Further research into these effector proteins and the creation of drug-responsive synthetic gene circuits may lead to the development of gene and cell +based aversion therapies for drug addiction. Growth Differentiation Factor 15 (GDF15), which contributes to vomiting and causes nausea, may be one such effector protein for inducing a conditioned aversion. The ability of synthetic gene circuits to train new functionalities into cells and their rapid evolution offer possibilities for the creation of engineered living therapeutics for the treatment of drug addiction. The idea of modifying addiction by the drug itself is offered; this enables the controlled release of therapeutic compounds in vivo and is believed to increase safety and patient compliance. Programmed gene switchesare created in response to illicit drugs. This will open up fresh possibilities for cutting-edge medicine and show significant potential for improving the effectiveness of drug addiction therapy. It would be crucial to do additional research in order to uncover designed artificial protein effectors and clarify novel signal transduction systems. Doing so would broaden the synthetic biology toolbox and enhance treatment plans for drug addiction.